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Review article

Enterochromaffin cell hyperplasia in the gut: Factors, mechanism and therapeutic clues

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ABSTRACT

Enterochromaffin (EC) cell is the main cell type that responsible for 5-hydroxytryptamine (5-HT) synthesis, storage and release of the gut. Intestinal 5-HT play a key role in visceral sensation, intestinal motility and permeability, EC cell hyperplasia and increased 5-HT bioavailability in the gut have been found to be involved in the symptoms generation of irritable bowel syndrome and inflammatory bowel disease. EC cells originate from intestinal stem cells, the interaction between proliferation and differentiation signals on intestinal stem cells enable EC cell number to be regulated in a normal level. This review focuses on the impact factors, pathogenesis mechanisms, and therapeutic clues for intestinal EC cells hyperplasia, and showed that EC cell hyperplasia was observed under the condition of physiological stress, intestinal infection or intestinal inflammation, the disordered proliferation and/or differentiation of intestinal stem cells as well as their progenitor cells all contribute to the pathogenesis of intestinal EC cell hyperplasia. The altered intestinal niche, i.e. increased corticotrophin releasing factor (CRF) signal, elevated nerve growth factor (NGF) signal, and Th2-dominant cytokines production, has been found to have close correlation with intestinal EC cell hyperplasia. Currently, CRF receptor antagonist, nuclear factor-κB inhibitor, and NGF receptor neutralizing antibody have been proved useful to attenuate intestinal EC cell hyperplasia, which may provide a promising clue for the therapeutic strategy in EC cell hyperplasia related diseases.

1. Introduction

Enterochromaffin (EC) cell, the most abundant enteroendocrine cell type in the gastrointestinal (GI) tract, is the main cell type responsible for 5-hydroxytryptamine (5-HT) synthesis, storage and release in the gut. It is reported that about 95% of the total 5-HT in the human body is found in the GI tract with 90% in EC cells [1]. 5-HT is synthesized in EC cells using the dietary L-tryptophan by the rate limiting enzyme tryptophan hydroxylase, intestinal 5-HT play a key role in visceral sensation, intestinal motility and permeability [2]. Currently, the increased intestinal EC cells and the elevated 5-HT bioavailability have been found to have close correlation with the pathogenesis of visceral hyperplasia and motility dysfunction [3,4], which were found in a number of pathological conditions of the GI tract, such as irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), and irritable pouch syndrome [5–8]. Considering the important role of EC cells and 5-HT signaling in GI functions, it is proposed that reducing intestinal 5-HT bioavailability (i.e. synthesis, release, or uptake) may be a novel strategy for alleviating the symptoms of functional GI disorders, such as IBS and IBD [9]. However, the pathological mechanism of intestinal EC cell hyperplasia is still unknown, no strategy can be used, to date, to attenuate intestinal EC cell hyperplasia. The role of increased EC cells in the pathogenesis of intestinal diseases have been extensively summarized in previous reviews [10,11], therefore will not be addressed here. This review will focus on the impact factors, pathogenesis mechanisms, and therapeutic clues on intestinal EC cells hyperplasia.

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2. Origin, localization and function of EC cells

It is well known that intestinal epithelial cells originate from multipotent intestinal stem cells. With the continuous proliferation and differentiation regulated mainly by the interaction of Wnt, Notch, and bone morphogenetic protein signaling pathways [12], the intestinal stem cells are finally differentiated into four distinct intestinal cell types, i.e. enterocytes, goblet, enteroendocrine and Paneth cells [13]. As the major cell type of intestinal enteroendocrine cells, EC cells are actively replenished from stem cells throughout life, become mature and migrate up the villous tips where they are eventually extruded [14]. It is generally accepted that the normal EC cells are a terminally differentiated and non-proliferating cell population. However, it is found that the turnover rate of intestinal EC cells varied largely, nearly 60–65% of EC cells were relatively rapidly renewing with a turnover rate about 16 days, while a relatively slowly renewing fraction (35–40%) was in an estimated turnover rate of approximately 150 days, which were both much slower than that of the surrounding enterocytes (3 ~ 4 d) [15].

EC cells are dispersed in the mucosa throughout the GI tract with different cells density: numerous EC cells are presented in the colon (~43%) and small intestine (~22% in ileum and ~20% in jejunum) in humans [16], while in rats, EC cells are predominantly located in the cecum (~$14 \times 10^3/mm^3$ mucosa) with a declining trend from proximal colon (~$12 \times 10^3/mm^3$ mucosa) to the distal colon (~$2.5 \times 10^3/mm^3$ mucosa) [17]. The triangular-shaped EC cells are located within the epithelium with the apex extending out into the lumen and the base in contact with the basement membranes. It is found that the microvilli extended in the lumen enable EC cells to transmit luminal stimuli, and thus EC cells are also regarded as the intestinal chemical and mechanical sensors [4,18].

The newly synthesized 5-HT is packaged in the secretory granules within EC cells. Upon stimulation (i.e. intraluminal distension, vagal-nerve stimulation, ingestion of a meal, or bile acids exposure), 5-HT is released from the secretory granules near the basal border or apical membrane of the EC cells [19]. The released 5-HT mediates multiple GI functions involving secretion, vasodilation and perception of pain, through activating a diverse family of 5-HT receptors on intrinsic and extrinsic afferent nerve fibers of gut [20]. A portion of 5-HT secreted from EC cells can also pour into the bloodstream, and then to be stored within the dense granules of platelets. Currently, the EC cell-derived 5-HT in circulation has been considered as an endocrine hormone that responsible for the inhibition of osteoblasts proliferation and the promotion of hepatic regeneration [21]. In EC cells, there are a variety of paracrine/hormonal substances co-stored with 5-HT, such as chromogranin A, melatonin, gamma-aminobutyric acid, and even corticotropin-releasing hormone [22]. The presence of chromogranin A enables enteroendocrine and EC cells to be identified by silver staining [23], and chromogranin A also plays regulatory role in the intestinal immune activation, inflammation, and enteroendocrine cells function [24]. Melatonin is biosynthesized from dietary amino acid tryptophan through a 5-HT pathway, in which 5-HT is converted to N-acetyl 5-HT and then ultimately converted to melatonin by the enzyme, acetylserotonin O-methyltransferase [25]. Melatonin is found to moderate visceral sensation and motility of the lower gut by acting on membrane melatonin receptors, and it is believed to function as a physiological antagonist of serotonin in the gut [26]. Corticotropin-releasing hormone within EC cells is considered to be involved in the modulation of the intestinal immune system and gastrointestinal functions during stressful conditions [27].

3. Factors affecting intestinal EC cell number

3.1. Physiological stress

Physiological stress is a specific term defined as the adaptive responses to psychological threats to an organism. Acute stress can evoke negative feedback to bring the body back to the homeostasis state, while chronic stress may become harmful for the destabilized homeostasis [28]. It is reported that about 60% of IBS patients have concomitant mood disorders (i.e. anxiety, depression), and mood disorders and increased EC cells were both important predictors of developing IBS [29,30]. Currently, evidence from accumulated clinical studies found that physiological stress, such as post-traumatic stress disorder, neonatal stress, depression, and anxiety, all contributed to the development of IBS syndrome [31], and increased 5-HT availability contributes to the development of abdominal pain of IBS [32]. Results from experimental studies confirmed that early-life stress induced EC cell hyperplasia in the gut of adult animals [33–35], and chronic restraint stress elevated the 5-HT content in the colon tissue [36]. When the animals were subjected to acute or protracted immobilization stress, increased EC cells were observed in the duodenum [37]. These results all indicated that physiological stress may be one of the pathogenic factors causing EC cell hyperplasia of gut.

Currently, even though the pathogenesis mechanism about EC cell hyperplasia is still unclear, an experimental study provides important evidence about the relationship between early-life stress and EC cell hyperplasia. It is reported that early-life stress promoted the differentiation of epithelial stem cells toward secretory lineages in rodents [38], and thus resulted in hyperplasia of EC cells in the gut. Results from two different researches both showed that increased EC cells were from the expansion of intestinal stem cells compartment as well as the differentiational alteration of intestinal secretory progenitors, corticotrophin releasing factor (CRF) pathway and nerve growth factor (NGF) activated Wnt/β-catenin signaling and Notch signaling are all involved in early-life stress induced EC cell hyperplasia [35,38]. Given that the microenvironment around intestinal stem cells plays a vital role in the maintenance, self-renewal, and differentiation of epithelial cells in the gut [39], it is possible that the changes evoked by physiological stress may alter the microenvironment of intestinal stem cells.

It is well known that the CRF signaling system is one of the main stress-activated pathways by which the brain translates a stimulus into an integrated physical response [40]. In the gut, CRF is synthesized by colonic mucosal cells near the base of the crypts, intestinal CRF can modulate gastrointestinal function under stressful conditions through acting on CRF receptors [41]. As CRF receptors are found presented in intestinal stem cells, goblet cells, enteric nervous system, and the scattered cells of lamina propria [42], the effect of CRF-related peptides on epithelial cell differentiation is worthy of study. It is reported that acute or chronic stress promoted long-term alterations of CRF, which in turn increased the expression of NGF in intestinal mucosa and enhances the release of NGF from intestinal mast cells [43]. Our recent study discovered that early-life stress expanded intestinal stem cells compartment and enhanced stem cells differentiation into EC cells via NGF mediated Wnt/β-catenin signaling. Based on above the evidence, it seems that both CRF and NGF all contribute to the pathogenesis of psychological stress-induced EC cell hyperplasia in the gut.

3.2. Infection

Infectious enteritis is a common event in the gut, although it can be rapidly cured in most cases. However, the gastrointestinal symptoms in some patients can persist for many years [44]. Post-infectious irritable bowel syndrome (PI-IBS) is a subgroup of IBS in which the patients acquired their symptoms after an acute infection in the gut [3]. It is found that the number of EC cells significantly increases in the colonic specimens of PI-IBS patients after gastrointestinal infection, and the elevated EC cell count and 5-HT availability are associated with visceral symptoms [45]. Further studies showed that intestinal EC cell number is markedly increased after parasite infection (i.e. *Trichinella spiralis*, *Trichuris muris, Hymenolepis diminuta*) in rodents with elevated 5-HT content and release [46], which is correlated with motility dysfunction

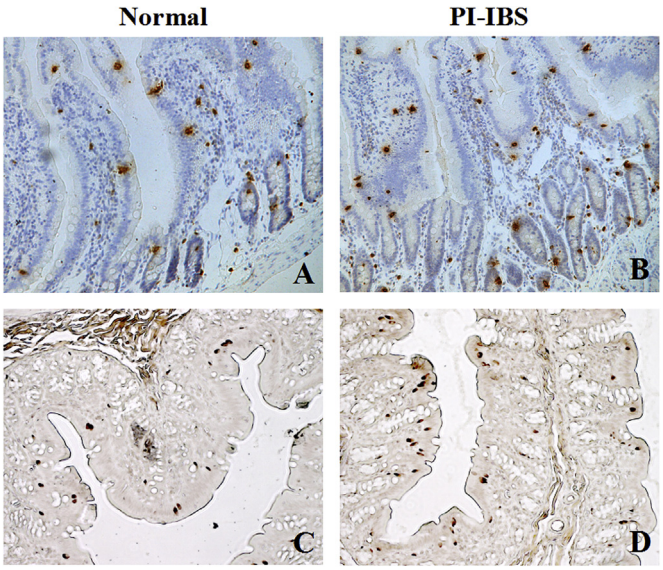

Fig. 1. Representative EC cells from the ileum and colon tissue of normal rats and post-inflammatory irritable bowel syndrome (PI-IBS) rats. The chemical agent TNBS was used to establish PI-IBS rat model, and the methods for model induction was described in the published article (HY Qin et al. World J Gastroenterol, 2012). Panel A and B were from ileum tissue (DAB staining, anti-serotonin immunostaining); panel C and D were from proximal colon tissue (silver staining).

and visceral hyperalgesia [47]. Moreover, intestinal infection caused by *Citrobacter rodentium*, *Campylobacter spp.* or *Shigella* was reported to increase EC cells and 5-HT release in the gut of rodents and Rhesus Macaques [48–50].

It is well known that infection leads to a marked inflammatory response, the results from clinical studies indicate that the inflammatory response to infection, rather than the infective organism itself, is the important factor for the development of intestinal symptoms [51]. In an animal model of post-inflammatory IBS, EC cell hyperplasia was also observed in the intestine (Fig. 1), the increased EC cell density was always accompanied with elevated 5-HT content and disrupted inflammatory cytokine production in colon tissue [52–55]. Data from experimental study showed that EC cell hyperplasia induced by parasite infection was accompanied with infiltration of mast cells and T lymphocytes in the lamina propria [47], while infection-induced EC cell hyperplasia presented with decreased expression of interleukin-4 and interleukin-13 [50], indicating that intestinal immune systems may influence EC cell number. One study using *Trichuris muris*-infected immunodeficient mice found that interleukin-13 plays a vital role in the development of EC cell hyperplasia under enteric infection via acting on interleukin-13 receptor expressed in EC cells [56]. Results from experimental studies reported that EC cell hyperplasia induced by parasite infection is T lymphocyte-dependent, and the infection-induced up-regulation of EC cells is attenuated in T cell receptor knockout mice [47]. Moreover, increased EC cell number and 5-HT content were found in the mice treated with in-vitro polarised T helper (Th) 2 cells or the mice with impaired Th1 cytokine production, indicating that EC cell number has a close correlation with intestinal Th1/Th2 balance [57]. In vitro studies also showed that interferon-γ and interferon-β, the key cytokines of Th1 response, significantly inhibit the proliferation of EC cell models, such as BON cells and QGP-1 cells [58–60]. The above evidence all indicated that EC cell number may be influenced by Th1 or Th2 cytokine-predominant environments and Th1-related cytokine may contribute to the development of EC cell hyperplasia in the gut.

3.3. Inflammation

IBD is the most common and serious chronic inflammatory bowel condition of the human, which is associated with dysregulation of mucosal immune system. Mucosal alteration of IBD is characterized by ulcerative lesions accompanied by infiltration of T lymphocytes, macrophages, neutrophils, and EC cells [61]. 5-HT has been found to play a key role in pathogenesis of colitis [11,62]. Evidence from clinical studies showed that colonic EC cells density was markedly elevated in patients with lymphocytic colitis, Crohn's ileitis, and Crohn's disease in remission [63–66], and these patients also experienced IBS-like symptoms. Results from experimental studies showed that the density of EC cells in the mucosa of proximal and distal colon are markedly increased in colitis animal model of rodents [67–69], which is accompanied with an increase of 5-HT content in the colon tissue [70–72]. Results from ileitis animal model also showed that the numbers of EC cells as well as goblet cells are all significantly increased in the inflamed ileum, indicating that the alteration of intestinal cells resulted from chronic inflammation is not only limited to EC cells [73].

Although most of EC cells are terminally differentiated, non-proliferating cell population in the gut, a small portion of EC cells may retain proliferative capacity during intestinal inflammation [73]. This study using an ileitis model of guinea pig found that the increased EC cells are distributed in the BrdU-labelled mucosa zone, but not in the un-labelled zone, indicating that EC cell hyperplasia may occur at the level of the stem cells or progenitor cells [73]. Previous studies also showed that EC-like cells in the stomach possess self-replicative capacity under the stimulation of lipopolysaccharide or gastrin [74], suggesting that the proliferative capacity of EC cells may be triggered or enhanced under certain stimuli, such as inflammation. Interestingly, a recent study reported that EC cells were increased along with decreased intestinal stem cells and their early progeny cells in colitis rats, and these alterations could be reversed by anti-inflammatory agents, indicating that inflammatory processes might interfere with the differentiation of secretory lineage [75]. Based on these evidence, it seems that intestinal EC cells hyperplasia induced by inflammation is correlated with the proliferation and/or differentiation of intestinal stem cells.

4. Pathological mechanism of EC cells hyperplasia

To date, the pathological mechanism of intestinal EC cell hyperplasia is still unknown, but it is proposed that the increased EC cell number might arise from increased division from stem cells, or increased EC cell progenitors [29]. Knowing that the special microenvironment around intestinal stem cells is termed as “niche”, niche plays a key role in intestinal stem cells maintenance, proliferation and differentiation [76]. Thus, it is possible that EC cell hyperplasia triggered by certain conditions (i.e. early-life stress, intestinal infection or intestinal inflammation) may result from the alteration of intestinal niche.

Intestinal niche is composed of a group of cells (i.e. myofibroblasts, endothelial cells, neural cells, Paneth cells, lymphocytes, macrophages and smooth muscle cells) as well as the intracellular signaling molecules (i.e. Notch, Wnt, etc.) giving out from the support cells [77,78]. Notch signaling regulates both progenitor cells proliferation and cellular differentiation. It is reported that early life stress-induced intestinal EC cell hyperplasia may result from the alteration of Notch signaling pathway via activating on CRF receptors [38]. In that study, it is found that early life stress-induced increase in EC cells in mice is coupled with decreased expression of neurogenin3 and increased expression of pancreatic and duodenal homeobox 1 (Pdx-1). It is well known that neurogenin3 and Pdx-1 are both the downstream genes of the Notch signaling cascade, Neurogenin3 is required for endocrine cell fate specification, while Pdx-1 is responsible for the specification of enteroendocrine cell types [14]. Results from our recent study showed

that early-life stress induced EC cell hyperplasia is resulted from the amplifying Wnt signaling, elevated intestinal NGF production and increased expression of NGF receptor tropomyosin receptor kinase A (TrkA) were triggered by early life stress [35]. In this study, we found that NGF directly targets intestinal stem cells, promoting their expansion and differentiation by *trans*-activating Wnt/β-catenin signaling, and thus leading to intestinal EC hyperplasia. Based on above findings, it seems that the dysfunction of Wnt and Notch signaling pathways both leads to the proliferative and differential alterations of intestinal stem cells, and thus resulted in EC cell hyperplasia under physiological stress, CRF and NGF play important regulatory roles in the renewal and differentiation of intestinal stem cells during pathological conditions.

It is notable that there are two studies using mouse model infected with *Trichuris muris* to investigate the relationship of T lymphocytes infiltration and EC cell hyperplasia, results from these studies showed that immunological cytokines, such as interleukin-13 from $CD4^+$ T cells, regulate EC cell number by acting directly on the specific cytokine receptors in EC cells [56,79], indicating the immunity-mediated control in epithelial homeostasis and EC cell biology. Another study investigating the Th1/Th2-based immuno-regulation of EC cells in the mice suffered from enteric infection showed that EC cell number was increased in Th2-dominant environment (abundant with interleukin-4 and interleukin-13) [57], indicating that the alteration of intestinal niche indeed plays an important role in the pathogenesis of EC cell hyperplasia. Findings from ileitis animal model showed that intestinal inflammation leads to the increase in EC cells, which may result from the acquired-proliferative capacity of stem cells or increased differentiation of postmitotic cells into EC cells [73]. It is also reported that intestinal secretory progenitor cells regain stem cell properties and generate all secretory cell types upon radiation damage in mice [80], indicating the importance of niche in regulating and maintaining intestinal homeostasis. Based on the above evidence, it seems that intestinal infection/inflammation could induce microenvironment alteration of stem cells, which may contribute to the development of EC cell hyperplasia. The impacts of early-life stress, intestinal infection or inflammation on EC cells density were summarized in Table 1, and the pathological mechanism concerning the proliferation and differentiation of intestinal stem cells and their progenitors are summarized in Fig. 2.

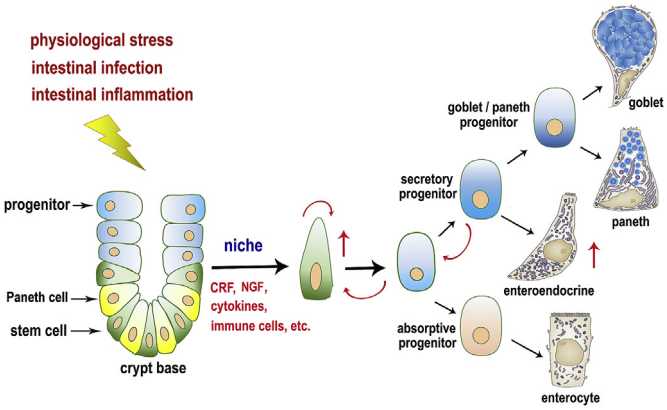

Fig. 2. Impact of physiological stress, intestinal infection, and intestinal inflammation on the proliferation and differentiation of intestinal stem cells and their progenitors. Physiological stress, intestinal infection, and intestinal inflammation triggered the alteration of intestinal niche, i.e. enhanced CRF signal, elevated NGF signal, increased Th2-dominant cytokines production, and dysregulated immune cells, etc. The proliferation capacity of intestinal stem cells was increased, while secretory progenitors also regained stem cell properties under the alteration of intestinal niche. Dysregulated proliferation and differentiation of intestinal stem cells and their progenitors all contribute to the increased EC cell number in the gut. *CRF*: corticotrophin releasing factor; *EC*: Enterochromaffin; *NGF*: nerve growth factor; *Th 2*: T help 2.

5. Potential therapeutic strategies for EC cells hyperplasia

Considering the important role of 5-HT in GI functions, drugs that target 5-HT signaling molecules, such as TPH inhibitor and 5-HT3 receptor antagonists, are found effective at alleviating the symptoms of functional GI disorders, such as IBS [9]. These strategies mainly focus on reducing intestinal 5-HT availability, but have no effect on EC cell number. As EC cells are the main source of intestinal 5-HT, understanding the pathogenesis mechanism underlying EC cell hyperplasia may provide clues for discovering the therapeutic strategies. Based on the evidence from experimental studies, it seems that EC cell hyperplasia has a close correlation with the increased proliferation and/or differentiation of intestinal stem cells, while the alterations of intestinal niche, such as CRF, NGF as well as lymphocytes, may contribute to these abnormalities.

Previous study showed that astressin, a CRF receptor antagonist, attenuates chronic psychological stress-induced intestinal EC cell hyperplasia via modifying the specification of secretory epithelial lineages in the gut [38]. Results from our recent study showed that the increased intestinal EC cells induced by early life stress could be reversed by intraperitoneal administration of MNAC13, a well-characterized anti-TrkA monoclonal antibody in mice [35]. All these results indicating that CRF and NGF may be the novel targets for managing stress-induced EC cell hyperplasia, inhibition of CRF or NGF signals may be the

Table 1
Impact factors associated with intestinal EC cell hyperplasia.

Impact factors		Objects	EC cells	Position	References
Physiological stress	Early life stress	Rats	↑	Colon &Duodenum	33, 34, 35,37
	Protracted Immobilization	Rats	↑	Duodenum	36
Infection	*Shigellosis*	Human	↑	Colon	47
	Campylobacter spp. & trichomonad	Rhesus Macaques	↑	Colon	48
	Hymenolepis diminuta	Mice	↑	Small intestine	44
	Trichinella spiralis	Mice	↑	Duodenum & jejunum	45
	Citrobacter rodentium	Mice	↑	Small intestine	46
	Trichuris muris	Mice	↑	Jejunum	54, 55
Inflammation	Colitis	Human	↑	Colon	61, 62, 63
	Ileitis	Human	↑	Ileum	64
	Acute ileitis[a]	Guinea-pigs	↑	Ileum	71
	Acute colitis[a]	Guinea-pigs/Rats	↑	Colon	66, 73
	Chronic colitis[b]	Rats/Mice	↑	Colon	68, 67, 65, 69, 70
	Post colitis[c]	Rats	↑	Colon	50, 51, 52, 53

[a] Acute ileitis/colitis: ileitis/colitis ≥ 7 days.
[b] Chronic colitis: colitis ≥ 14 days.
[c] Post colitis: complete recovery from colitis.

important therapeutic strategies for the treatment of EC cell hyperplasia-associated gastrointestinal diseases. Further investigations found that EC cell number is influenced by Th1 or Th2 cytokine predominant environment, and Th1 environment (abundant with interferon-γ) attenuated infection-induced EC cell hyperplasia in mice [57]. One study based on colitis rats revealed that inflammation-induced EC cell hyperplasia was reversed by anti-inflammatory agents, i.e. nuclear factor-κB inhibitor, via restoring stem cells and their progenitors [75]. All this evidence indicated that the regulation of intestinal immune-endocrine axis may be a strategy against infection/inflammation-induced EC cell hyperplasia.

6. Conclusion and perspective

Evidence from clinical and experimental studies all showed that intestinal EC cell hyperplasia and elevated 5-HT bioavailability have a close correlation with intestinal GI disorder, such as visceral hyperplasia, motility and mucosal barrier dysfunction. Nowadays, intestinal EC cell hyperplasia and elevated 5-HT content has been considered as the key factors for the pathogenesis of IBS and IBD. Accumulated evidence indicated that EC cells hyper-proliferation under the condition of physiological stress, intestinal infection (i.e. bacteria, viruses and parasites), and even intestinal inflammation, increased CRF signal, elevated NGF signal, as well as Th2-dominant cytokines production contributed to the altered proliferation and/or differentiation of stem cells or their progenitor cells in the gut, suggesting the important role of intestinal niche in the pathogenesis of EC cell hyperplasia. Based on current evidence, altered intestinal Wnt as well as Notch signaling pathways were found to have close correlation with EC cell hyperplasia. Nowadays, CRF receptor antagonist, nuclear factor-κB inhibitor, anti-TrkA antibody and interferon-γ may be useful to attenuate intestinal EC cell hyperplasia.

With the rapid growth in the understanding of intestinal stem cells, the important role of intestinal stem cells in the pathogenesis of intestinal disease has been elucidated [81], therapies based on intestinal stem cells were also studied timely [82]. This review summarized the main factors affecting intestinal EC cell number, the possible underlying mechanism may involve dysregulation in the proliferation and differentiation of intestinal stem cells. Even though, there are still many areas remain nebulous, i.e. whether the affecting factors (early-life stress, infection or inflammation) interact with each other in the pathogenesis of EC cell hyperplasia? Whether these signaling pathways that responsible for intestinal EC cell hyperplasia overlaps? Whether the two intestinal stem cell pools (rapid cycling & quiescent) were both affected under these affecting factors? All these remain to be demonstrated, and more studies are needed in the future.

Declaration of competing interest

No conflicts of interest, financial or otherwise, are declared by the authors.

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